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Health effects of exposure to residential air pollution in patients with pulmonary arterial hypertension: A cohort study in Belgium

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Take home message:

This retrospective cohort study showed that both exercise capacity and the ESC/ERS risk assessment were associated with previous exposure to air pollutants in PAH patients. In contrast to previous data, no significant association with adverse outcome and mortality was found.

To the editor,

We read with interest the paper by Sofianopoulou *et al.* (1). The authors have significantly contributed to highlight the potential link between air pollution and health outcomes among pulmonary arterial hypertension (PAH) patients, by showing that, exposure to particulate matter with an aerodynamic diameter smaller than 2.5 µm ($PM_{2.5}$) was significantly associated with transplant-free survival, and traffic-related air pollution was correlated with the European Society of Cardiology (ESC)/ European Respiratory Society (ERS) risk categories and haemodynamics at baseline.

In this letter we would like to report our results exploring a potential association between exposure to residential $PM_{2.5}$, PM_{10}, nitrogen dioxide (NO_2), black carbon (BC), traffic-related air pollution, and parameters related to prognosis, pathophysiology, progression and survival in a cohort of PAH patients.

Consecutive patients with a hemodynamically proven diagnosis of idiopathic/heritable/anorexigen (IHA)-PAH between January 1995 and September 2018 and long-term follow-up (at least two follow-up visits) at University Hospitals of Leuven (median follow-up of 4.8 years) were included (**Figure 1a**). To assess exposure to air pollution, each residential address at baseline visit was geocoded and linked with annual average levels of $PM_{2.5,}$ PM_{10}, NO_2 and BC (year 2015), estimated with land use regression models, as previously described (2). In addition, traffic-related exposure was determined based on the distance between the residence and the nearest major roads. Multivariate Cox regression was applied to model the association with survival and adverse outcome including PH-related hospitalization or treatment with i.v./s.c. prostanoids or lung transplantation. We used multivariate linear regression modelling for six-minute walk distance (6MWD), right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), cardiac index (CI), pulmonary vascular resistance (PVR) and circulating levels of C-reactive protein (CRP) at diagnosis. Multivariate ordinal logistic regression was used for New York Health Association Functional Class (NYHA FC) and an abbreviated version of the ESC/ERS risk stratification (3). We adjusted for age, gender, body mass index, smoking habits and level of obtained education. Additional adjustment for treatment with i.v./s.c. prostanoids and presence of bone morphogenetic protein receptor 2 mutations did not modify our results. The patient population was further stratified by i) age (younger than and older or equal to 65 at diagnosis), considering that elderly individuals have been exposed for a longer time and may experience greater risk of adverse outcome when exposed to air pollution, and ii) aetiology (only patients with IPAH and HPAH). The associations are shown per increase of 10 $\mu g \cdot m^{-3}$ for $PM_{2.5}$, PM_{10} and NO_2, per increase of 1 $\mu g \cdot m^{-3}$ for BC and per interquartile range increase (IQR, 1338m) for the distance to major roads. To control for type I errors and to adjust for the overall false positive rate, the p-values were Bonferroni corrected accounting for at least five multi-comparisons.

A total of 211 patients (37% male) were studied with median age of 57 years. Patients displayed a severe hemodynamic profile and reduced exercise capacity (Figure 1a). During the observation period, 29% of the patients were treated with i.v./s.c. prostanoids, 12% underwent a lung transplantation and 53% of the patients died (not mutually exclusive, **Figure 1a**).

Multivariate Cox-regression analysis showed that exposure to residential air pollution was not significantly associated with death or with any of the composite endpoints of adverse outcome. Multivariate linear

regression modelling for 6MWD, RAP, mPAP, CI, PVR and CRP circulating levels at diagnosis, showed that only 6MWD was significantly associated with the distance from the patients' home to a major road (estimate was 27.7 meters, 95% CI 1.7- 52.5 per IQR change) **(Figure 1b)**. Finally, multivariate ordinal logistic regression revealed additional associations between the ESC/ERS risk score and exposure levels of BC (OR 3.9 95% CI 1.3-11.5) and NO_2 (OR 1.9 95% CI 1.1-3.2) in the subgroups of patients with IPAH and HPAH **(Figure 1c)**.

The study of Sofianopoulou *et al.* was the first to report that mortality of PAH patients is associated with ambient air pollution (1). However, we did not confirm this finding in our cohort. The discrepancies between our results and those by Sofianopoulou *et al.* may have various reasons, including: i) difference in the sample size; ii) inclusion of drug related PAH, with anorexigen exposure appearing as a potential effect modifier, blurring the association of ESC/ERS risk score with air pollution; iii) a higher proportion of patients with an event, due to longer inclusion and follow-up periods; vi) differences in exposure concentrations and mean distance to major roads.

The concept that air pollution may provoke changes in the pulmonary vasculature leading to PH, is biologically plausible given the proximity of the pulmonary vasculature and the alveolar-capillary interface and the potential for pollution to either act directly or through translocation into the circulation to elicit inflammation, oxidative stress and coagulation responses (4–6). Evidence from animal models and epidemiological cohort studies suggests that air pollution exposure, including particulate matter and diesel exhaust, results in changes to the pulmonary vasculature (7–11). We showed that living far from a major road may have beneficial effect on exercise capacity and found a significant association between the ESC/ERS risk score and exposure to NO_2 and BC, pollutants mainly present in vehicle exhaust emissions. The strength of our study is the large cohort of PAH patients with a close follow-up and uniform measures of air pollution exposure. A limitation of the study is the usage of a proxy marker for traffic pollution and the fact that exposure variables do not take into account individual differences in the time spent at home, work or in other environments, although PAH patients may spend more time at home than the general population. In addition, even applying Bonferroni correction, known to decrease type I errors and increase type II errors, associations remained significant.

In conclusion, in contrast to findings by Sofianopoulou *et al.,* we found that exposure to $PM_{2.5}$, PM_{10}, NO_2, BC and residential distance to major roads are not related to adverse outcome or mortality in PAH. Importantly, we did find a significant association between NO_2, BC and ESC/ERS risk score, similarly to the observations in the UK. We also observed an association between improved exercise capacity and living far from a major road. However, we believe that more data need to be collected to better document the compelling debate on air pollution and PAH.

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Conflict of interest: The authors declare that they have no conflict of interest.

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Legend to Figure

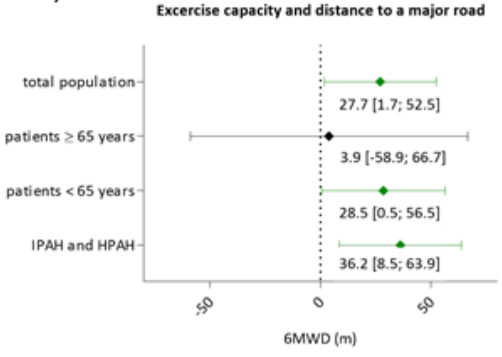
Figure 1. a) Table summarizing patient characteristics at baseline; values are expressed as mean ± standard deviation for continuous variables or number of patients and percentages for categorical variables. PAH: pulmonary arterial hypertension, RAP: right atrial pressure, CI: cardiac index, PVR: pulmonary vascular resistance, mPAP: mean pulmonary arterial pressure, BMI: body mass index, NYHA FC: New York Heart Association functional class, ESC/ERS: European Society of Cardiology and European respiratory Society, 6MWD: six-minute walking distance, IV: intravenous; **b**) Association of the six-minute walk distance and the distance to a major road in PAH patients; **c**) Association of the ESC/ERS risk score and residential pollution in PAH patients. Associations are adjusted for age, gender, BMI, smoking and socio-economic status. Total population (n= 211), patients ≥ 65 years (n=72), patients < 65 years (n=139), IPAH and HPAH (n=179). IPAH: idiopathic pulmonary arterial hypertension, HPAH: heritable pulmonary arterial hypertension, 6MWD: six-minute walk distance, ESC/ERS: European Society of Cardiology, ERS: European Respiratory Society, BC: Black Carbon NO_2: Nitrogen Dioxide; Results are expressed as beta estimates [95% confidence interval] per interquartile range increase (1338m) for the distance to a major road, and expressed as Odds Ratio (OR) [95% confidence interval] per increase of 10 $\mu g \cdot m^{-3}$ for NO_2 and per increase of 1 $\mu g \cdot m^{-3}$ for BC.

a)

Characteristics	Cohort n= 211
idiopathic PAH, n (%)	158 (75)
heritable PAH, n (%)	21 (10)
PAH associated to appetite suppressants, n (%)	32 (15)
median age at diagnosis, years (interquartile range)	57 [37; 69]
male sex, n (%)	78 (37)
mean RAP, mmHg ± SD	9 ± 5
mean CI, L/min per m^2 ± SD	2.1 ± 0.6
mean PVR diagnosis, dyn.s.cm^{-5} ± SD	988 ± 463
mean mPAP, mmHg ± SD	51 ± 11
mean BMI, kg/m^2 ± SD	26 ± 6.7
Smoking habits, n =196	
never, n (%)	120 (61.2)
active, n (%)	16 (8.2)
ex-smokers, n (%)	60 (30.6)
NYHA FC, n (%), n=162	
I	4 (2.5)
II	41 (25.3)
III	93 (57.4)
IV	24 (14.8)
Degree level of professional education, n=127	
no education after high school, n (%)	85 (66.9)
short education after high school, n (%)	34 (26.8)
university education, n (%)	8 (6.3)
ESC/ERS risk score at diagnosis (Kylhammar) (47)	
low risk, n (%)	49 (23)
intermediate risk, n (%)	141 (67)
high risk, n (%)	21 (10)
mean 6MWD, m ± SD	322 ± 146
IV treatment, n (%), n=210	61 (29)
transplantation, n (%)	25 (12)
deceased, n (%)	112 (53)
median survival time, years (interquartile range)	4.8 [1.85; 11.91]
yearly median level of particulate matter ≤ 2,5 µm, µg/m^3 (interquartile range)	12.0 [11.3; 12.9]
yearly median level of particulate matter ≤ 10 µm, µg/m^3 (interquartile range)	18.3 [17.1; 19.8]
yearly median level of nitrogen dioxide, µg/m^3 (interquartile range)	16.9 [13.9; 21.7]
yearly median level of black carbon, µg/m^3 (interquartile range)	1.02 [0.9; 1.2]
median distance to major road, meter (interquartile range)	726.9 [33.5; 1653.1]

Values are expressed as mean ± standard deviation for continuous variables or number of patients and percentages for categorical variables. PAH: pulmonary arterial hypertension, RAP: right atrial pressure, CI: cardiac index, PVR: pulmonary vascular resistance, mPAP: mean pulmonary arterial pressure, BMI: body mass index, NYHA FC: New York Heart Association functional class, ESC/ERS: European Society of Cardiology and European respiratory Society, 6MWD: six-minute walking distance, IV: intravenous.

b)



c)